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DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

44342.013500

U S APPLICATION NO (IF KNOWN, SEE 37 CFR

10/069192

INTERNATIONAL APPLICATION NO
PCT/JP00/02616

INTERNATIONAL FILING DATE
21 April 2000

PRIORITY DATE CLAIMED
23 April 1999

TITLE OF INVENTION

METHOD FOR PULVERIZING TO FINE POWDER

APPLICANT(S) FOR DO/EO/US

NIPPON SHINYAKU CO., LTD.

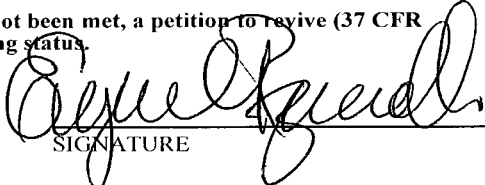
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☒ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☒ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)) (**Executed**)
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter 2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4)
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Copy of the first page of the published International Application Number WO00/64875.

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.53) 10/069192		INTERNATIONAL APPLICATION NO. PCT/JP00/02616		ATTORNEY'S DOCKET NUMBER 44342.013500					
24. The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) : <input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1040.00 <input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$890.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 ENTER APPROPRIATE BASIC FEE AMOUNT =				CALCULATIONS PTO USE ONLY <table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:50%;">\$890.00</td> <td style="width:50%;"></td> </tr> <tr> <td>\$0.00</td> <td></td> </tr> </table>		\$890.00		\$0.00	
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Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:50%;">\$0.00</td> <td style="width:50%;"></td> </tr> </table>		\$0.00			
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CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE						
Total claims	7 - 20 =	0	x \$18.00	\$0.00					
Independent claims	2 - 3 =	0	x \$84.00	\$0.00					
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>				\$0.00					
TOTAL OF ABOVE CALCULATIONS =				\$890.00					
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				\$0.00					
SUBTOTAL =				\$890.00					
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).				\$0.00					
TOTAL NATIONAL FEE =				\$890.00					
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).				\$40.00					
TOTAL FEES ENCLOSED =				\$930.00					
				Amount to be: refunded	\$				
				charged	\$				
a. <input type="checkbox"/> A check in the amount of _____ to cover the above fees is enclosed. b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. 50-1561 in the amount of \$930.00 to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-1561 A duplicate copy of this sheet is enclosed d. <input type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.									
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.									
SEND ALL CORRESPONDENCE TO:									
Eugene C. Rzucidlo, Esq. GREENBERG TRAURIG, LLP 885 Third Avenue, 21st Floor. New York, New York 10022 Telephone Number: 212-801-2146 Facsimile Number: 212-688-2449			 SIGNATURE Eugene C. Rzucidlo NAME 31,900 REGISTRATION NUMBER 10/23/01 DATE						

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特許協力条約に基づいて公開された国際出願



(51) 国際特許分類7 C07D 213/89, A61K 31/4409, A61J 3/02, A61P 35/00	A1	(11) 国際公開番号 WO00/64875 (43) 国際公開日 2000年11月2日(02.11.00)
(21) 国際出願番号 PCT/JP00/02616 (22) 国際出願日 2000年4月21日(21.04.00) (30) 優先権データ 特願平11/116810 1999年4月23日(23.04.99) JP (71) 出願人 (米国を除くすべての指定国について) 日本新薬株式会社(NIPPON SHINYAKU CO., LTD.)(JP/JP) 〒601-8550 京都府京都市南区吉祥院西ノ庄門口町14番地 Kyoto, (JP) (72) 発明者 ; および (75) 発明者 / 出願人 (米国についてのみ) 幸 哲夫(YUKI, Tetuo)(JP/JP) 〒621-0012 京都府亀岡市大井町並河三丁目17-4 Kyoto, (JP) 渡辺修二(WATANABE, Shuji)(JP/JP) 〒524-0022 滋賀県守山市守山五丁目8-3 サムズ守山507号 Shiga, (JP) 工藤 等(KUDO, Hitoshi)(JP/JP) 〒520-0002 滋賀県大津市際川三丁目12-24 Shiga, (JP)		(81) 指定国 CA, CN, JP, KR, MX, RU, US, 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM) 添付公開書類 国際調査報告書 請求の範囲の補正の期限前の公開 ; 補正書受領の際には再公開される。
(54)Title: METHOD FOR PULVIRIZING TO FINE POWDER (54)発明の名称 微粉化法 (57) Abstract A method for pulverizing (E)-4-[2-[2-[N-acetyl-N-(4-methoxybenzenesulfonyl)amino]phenyl]ethenyl]pyridine-1-oxide to a fine powder, characterized as pulverizing it by means of an open-circuit grinding machine, for example, to a powder which has an average particle diameter in the range of 1 to 25 μm and contains particles having a particle diameter of 50 μm or more in an amount of 2 % or less. The method can be used for pulverizing the compound to a fine powder while maintaining the crystal form of the compound.		

44342.013500

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Tetuo YUKI, *et al.*

Serial No.: T/B/A

Group Art Unit: T/B/A

Filed: Herewith

Examiner: T/B/A

For: METHOD FOR PULVERIZING TO FINE POWDER

Assistant Commissioner for Patents
Box PCT
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to the calculation of the filing fee and examination of the above-referenced new United States Patent Application, please amend the present Application as follows.

IN THE CLAIMS:

Please cancel claims 1-6 without prejudice, and replace them with new claims 7-13 as provided herein.

7. A method of micronizing a (E)-4-[2-[2-[N-acetyl-N-(4-methoxybenzenesulfonyl)amino]phenyl]ethenyl]pyridine 1-oxide compound comprising the step of pulverizing the compound with an open-circuit pulverizing type mill.

8. The micronizing method of claim 7 wherein said open-circuit pulverizing type mill is either a high-speed rotary impact mill or a pneumatic mill.

9. The micronizing method of claim 7 wherein said compound is pulverized to a mean particle diameter of from 1 μm to about 25 μm with particles larger than 50 μm constituting a fraction of not more than 2% of a total number of particles.

10. The micronizing method of claim 8 wherein said compound is pulverized to a mean particle diameter of from 1 μm to about 25 μm with particles larger than 50 μm constituting a fraction of not more than 2% of a total number of particles.

11. A chemical composition comprising a plurality of crystalline (E)-4-[2-[2-[N-acetyl-N-(4-methoxybenzenesulfonyl)amino]phenyl]ethenyl]pyridine 1-oxide particles with a mean particle diameter of from 1 μm to about 25 μm with particles larger than 50 μm constituting a fraction of not more than 2% of a total number of particles.

12. A pharmaceutical composition comprising a therapeutically effective amount of the plurality of crystalline (E)-4-[2-[2-[N-acetyl-N-(4-methoxybenzenesulfonyl)amino]phenyl]ethenyl]pyridine 1-oxide particles of claim 11 as an active ingredient.

13. An anticancer drug comprising a therapeutically effective amount of the plurality of crystalline (E)-4-[2-[2-[N-acetyl-N-(4-methoxybenzenesulfonyl)amino]phenyl]ethenyl]pyridine 1-oxide particles of claim 11 as an active ingredient.

REMARKS

The present amendment has been made to delete multiple dependencies and otherwise bring the claims into conformance with United States patent practice, and to limit the fees. Early and favorable action is respectfully requested.

AUTHORIZATION

Please charge any required fee to the Greenberg Traurig Deposit Account No. 50-1561.

Respectfully Submitted,
Greenberg Traurig, LLP

Date: October 23, 2001

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DESCRIPTION

METHOD FOR PULVERIZING TO FINE POWDER

TECHNICAL FIELD

The present invention relates to a method of micronizing (E)-4-[2-[2-[N-acetyl-N-(4-methoxybenzenesulfonyl)amino]phenyl]ethenyl]-pyridine 1-oxide (hereinafter referred to as the present compound) which is a known substance having high antitumoral activity.

The present compound as such and its usefulness referred to above are described in detail in, inter alia, PCT WO95/27699.

BACKGROUND ART

In order to improve the absorption, solubility, content uniformity and AUC (bioavailability), among others, of a sparingly soluble drug, it is generally considered desirable to micronize the drug. Actually, for providing sparingly soluble drugs in the tablet or the like pharmaceutical dosage form, they are micronized into fine powders on many occasions.

The pulverizing systems for such micronization can be roughly classified into an open-circuit pulverizing system and a closed-circuit pulverizing system. The

open-circuit pulverizing system comprises passing a pulverization load a few times within one minute or substantially only once through a pulverizing zone and the closed-circuit pulverizing system comprises passing a pulverization load many a time during a comparatively long time through a pulverizing zone.

Meanwhile, drugs in general may usually remain in a thermodynamically stable state in a crystalline form than in a non-crystalline form and, therefore, in consideration of the stability of the drug, the pulverizate of the drug is preferably provided in a crystalline form barring special circumstances.

DISCLOSURE OF INVENTION

The present invention has for its object to provide a method of micronizing the present compound while maintaining its crystalline form and a finely-divided pulverizate of the present compound.

After intensive research the inventors of the present invention found that the above object can be accomplished by micronizing the present compound with a mill of the open-circuit pulverizing type and have accordingly developed the present invention.

The present invention, therefore, is directed to a method of micronizing the present compound characterized in that the present compound is

comminuted with a mill of the open-circuit pulverizing type.

The mill of said open-circuit pulverizing type which can be used in the present invention includes but is not limited to a high-speed rotary impact mill and a pneumatic mill.

Micronization of the present compound should be carried out to the extent that the mean particle diameter of the pulverizate will be 1~25 μm with 50 μm and larger particles accounting for 2% or less, preferably to the extent that all particles fall within the diameter range of 5~20 μm and particles not less than 50 μm in diameter account for 1% or less or even 0%. Accordingly, the crystalline form of the present compound (hereinafter referred to as the present pulverizate) with a mean particle diameter of 1~25 μm with 50 μm and larger particles constituting a fraction of not more than 2%, preferably with a mean particle diameter of 5~20 μm with 50 μm and larger particles constituting a fraction of not more than 1% or 0%, is also subsumed in the scope of the present invention.

When a high-speed rotary impact mill is used, the pulverization is preferably carried out at a rotational speed of not less than 10,000 rpm, particularly not less than 20,000 rpm, although the optimum pulverizing

condition depends on the type of machine and the drug lot, among other variables. When a pneumatic mill is used, the pulverization is preferably carried out at an air supply rate of 0.5~50 m³/min and a pressure of 3~7 kg/cm², particularly an air supply rate of 10~45 m³/min and a pressure of 5~6 kg/cm².

The micronization according to the invention can be easily accomplished by feeding the present compound to a mill of the open-circuit pulverizing type at a suitable rate (e.g. 10 g ~ 1,000 kg/hr) for micronization.

The present pulverizate can be used as a medicine in the same manner as the present compound, and a pharmaceutical composition comprising the present pulverizate as an active ingredient can be used as an anticancer drug in cancer of the lung, cancer of the mammary gland, cancer of the digestive tract, cancer of the prostate, and cancer of the blood, among other diseases.

The pharmaceutical composition (hereinafter referred to as the present composition) comprising the present pulverizate as an active ingredient can be manufactured by using the present pulverizate as it is alone or together with a pharmaceutically acceptable, nontoxic and inert carrier according to a formulation

including 0.1% ~ 99.5%, preferably 0.5% ~ 90%, of the pulverizate and can be administered to animals inclusive of man.

As said carrier, a solid, semisolid or liquid diluent, a filler, and one or more other formulation additives can be employed. The present composition is preferably administered in a unit dosage form. The present composition can be administered orally, parenterally, locally (transdermal delivery, instillation into the eye or pernasal delivery), or rectally, with the oral route being particularly preferred. Of course, a dosage form suited to the selected route of administration is employed.

The dosage of the present pulverizate for use as a medicine should be judiciously established in consideration of patient factors, e.g. age and body weight, the route of administration, the nature and severity of illness, indication and so on. Usually, however, the range of 1 mg ~ 500 mg/day, preferably 2.5 mg ~ 200 mg/day is appropriate for an adult human. Lower doses may be sufficient in some cases, while higher doses may be necessary in others. The above dosage can be administered in 2~4 divided doses a day.

BEST MODE FOR CARRYING OUT THE INVENTION

The following examples, comparative example, and

test examples illustrate the present invention in further detail.

Example 1

The bulk powder, 50 g, of the present compound (mean particle diameter 25.9 μm) was fed to a pin mill (Stud Mill 63C, Hosokawa Micron K.K.), a high-speed rotary impact mill of the open-circuit pulverizing type, by means of a load feeder screw at a rate of 100 g/hr and pulverized with a power supply of 200 V at a rotational speed of 20,000 rpm, and the pulverizate (the present pulverizate), 44.2 g, was recovered in a recovery bottle.

Example 2

The bulk powder, 230 g, of the present compound (mean particle diameter 24.2 μm) was fed to a hammer mill (Sample Mill AP-S, Hosokawa Micron K.K.), a high-speed rotary impact mill of the open-circuit pulverizing type, by means of a load feeder screw at a rate of 100 g/hr and pulverized with a power supply of 200 V at a rotational speed of 11,700 rpm, and the pulverizate (the present pulverizate), 205.9 g, was recovered in a recovery bottle.

Comparative Example 1

The bulk powder of the present compound (2 g; mean particle diameter 25.9 μm) was placed in the bowl (25

ml agate bowl, effective capacity 10 ml, number of balls 10, ball diameter 12 mm) of a planetary ball-mill (P-7, Fritsch Japan K.K.), a mill of the closed-circuit pulverizing type, and pulverized at 2,480 rpm for 2 hours to give 1.4 g of a pulverizate. In the course, the pulverizate was withdrawn at 30 minutes and 60 minutes of pulverization, ground in an agate mortar and about 0.2 g each of the resulting powders was taken as a sample.

Test Example 1

Determination of particle diameter

Twenty (20) mg each of the pre-pulverized present compound and the pulverizates of the compound as obtained in Examples 1 and 2 and Comparative Example 1 was taken in a test tube and 5 ml of silicone oil (product of Shin-Etsu Chemical Co.) was added. The mixture was stirred with a bench-top mixer for 20 seconds and further dispersed with a bench-top supersonic washer (UT-51N, product of Sharp Corporation) for 5 minutes. Then, the particle size distribution was determined with an ultracentrifugal automatic particle size distribution analyzer (CAPA-700, manufactured by Horiba, Ltd.). The results are shown in Table 1.

Table 1

	Before pulverization	After pulverization
--	-------------------------	------------------------

Example 1	Mean	25.9±43.3 μm	9.7±4.3 μm
	≥30 μm	35.5%	0%
	≥50 μm	20.4%	-
Example 2	Mean	24.2±31.2 μm	15.2±6.8 μm
	≥30 μm	26.6%	6.8%
	≥50 μm	12.8%	0%
Comparative Example	Before pulverization		
	Mean	25.9±43.3 μm	
	≥30 μm	35.5%	
	≥50 μm	20.4%	
	After pulverization		
	After 30 min. Mean	15.1 μm	
	After 60 min. Mean	12.4 μm	
	After 120 min. Mean	10.7±4.5 μm	
	≥30 μm	0%	
	≥50 μm	-	

Test Example 2

Confirmation of crystalline state

Using each of the unpulverized present compound and the pulverizates of the same compound as obtained in Examples 1 and 2 and Comparative Example 1, the powder X-ray diffraction pattern was recorded with a powder x-ray diffraction analyzer (RAD-2B, manufactured by Rigaku Denki). The results are shown in Figs. 1~3.

It will be apparent from the drawings that the pulverizates as micronized with a mill of the open-circuit pulverizing type retained the crystalline form, showing X-ray diffraction peaks. On the other hand, the pulverizate prepared with a mill of the closed-circuit pulverizing type showed a disappearance of X-ray diffraction peaks with the progress of pulverization and had changed to a non-crystalline compound showing

no X-ray diffraction peaks after a pulverization time of 60 minutes.

Test Example 3

Administration experiment (in vivo)

A capsule prepared using the unpulverized present compound and a capsule prepared using the pulverizate obtained in Example 1 (the present pulverizate) according to the physical blending formula shown in Table 2 were respectively administered orally to 4 crab-eating monkeys (male, aged 6~9 years). The blood was serially sampled and the plasma concentration of the metabolite of the present compound [(E)-4-[2-[2-[N-(4-methoxybenzenesulfonyl)amino]phenyl]-ethenyl]pyridine 1-oxide] was determined by HPLC. The results are shown in Fig. 4.

Table 2 (physical blending formula)

The present pulverizate	300 mg
Lactose	103 mg
Starch	44.5 mg
Avicel®	35 mg
Hydroxypropylcellulose SL	15 mg
Magnesium stearate	2.5 mg
<hr/>	
Total	500 mg

It will be apparent from Fig. 2 that the plasma concentration of the present compound can be

significantly increased by micronizing the compound.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows X-ray diffraction patterns relevant to Example 1. In the figure, the top row shows the X-ray diffraction pattern after pulverization and the bottom row shows the X-ray diffraction pattern before pulverization. The abscissa represents the diffraction angle ($^{\circ}$) and the ordinate represents the intensity (cps).

Fig. 2 shows X-ray diffraction patterns relevant to Example 2. In the figure, the top row shows the X-ray diffraction pattern after pulverization and the bottom row shows the X-ray diffraction pattern before pulverization. The abscissa represents the diffraction angle ($^{\circ}$) and the ordinate represents the intensity (cps).

Fig. 3 shows X-ray diffraction patterns relevant to Comparative Example 1. In the figure, the lowermost row shows the X-ray diffraction pattern before pulverization, the second lower row shows the X-ray diffraction pattern after 30 minutes of pulverization, the second upper row shows the X-ray diffraction pattern after 60 minutes of pulverization, and the uppermost row shows the X-ray diffraction pattern after 120 minutes of pulverization. The abscissa represents the

diffraction angle ($^{\circ}$) and the ordinate represents the intensity (cps).

Fig. 4 shows the plasma concentration time course of the metabolite of the present compound. -○- represents the result for the present compound micronized in accordance with the invention (the present pulverizate) and -●- represents the results for the present compound prior to micronization. The abscissa represents time (hrs) and the ordinate represents the plasma concentration ($\mu\text{g/ml}$) of the metabolite.

CLAIMS

1. A method of micronizing (E)-4-[2-[2-[N-acetyl-N-(4-methoxybenzenesulfonyl)amino]phenyl]ethenyl]pyridine 1-oxide characterized in that the compound is pulverized with a mill of the open-circuit pulverizing type.

2. The micronizing method defined in Claim 1 wherein said mill of the open-circuit pulverizing type is either a high-speed rotary impact mill or a pneumatic mill.

3. The pulverizing method defined in Claim 1 or 2 characterized in that said compound (drug) is pulverized to a mean particle diameter of 1~25 μm with 50 μm and larger particles constituting a fraction of not more than 2%.

4. A crystalline (E)-4-[2-[2-[N-acetyl-N-(4-methoxybenzenesulfonyl)amino]phenyl]ethenyl]pyridine 1-oxide having a mean particle diameter of 1~25 μm with 50 μm and larger particles constituting a fraction of not more than 2%.

5. A pharmaceutical composition comprising the crystalline (E)-4-[2-[2-[N-acetyl-N-(4-methoxybenzenesulfonyl)amino]phenyl]ethenyl]pyridine 1-oxide defined in Claim 4 as an active

Abstract

The present invention has for its object to provide a method of micronizing (E)-4-[2-[2-[N-acetyl-N-(4-methoxybenzenesulfonyl)amino]phenylethenyl]pyridine 1-oxide while maintaining its crystalline.

The present invention relates to a method of micronizing the above compound characterized in that the compound is comminuted, for example, to the extent that the mean particle diameter of the compound will be 1~25 μm with 50 μm and larger particles accounting for 2% or less with a mill of the open-circuit pulverizing type.

1 / 2

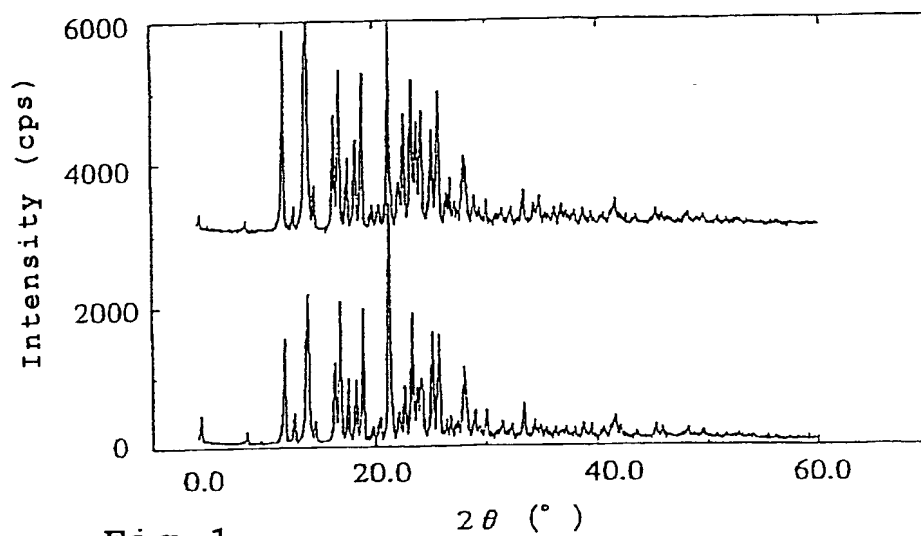


Fig. 1

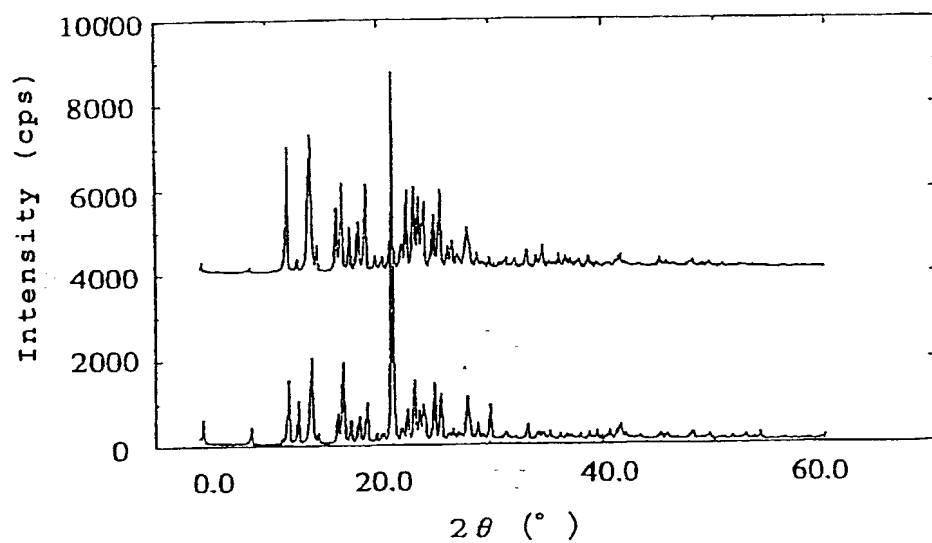


Fig. 2

2 / 2

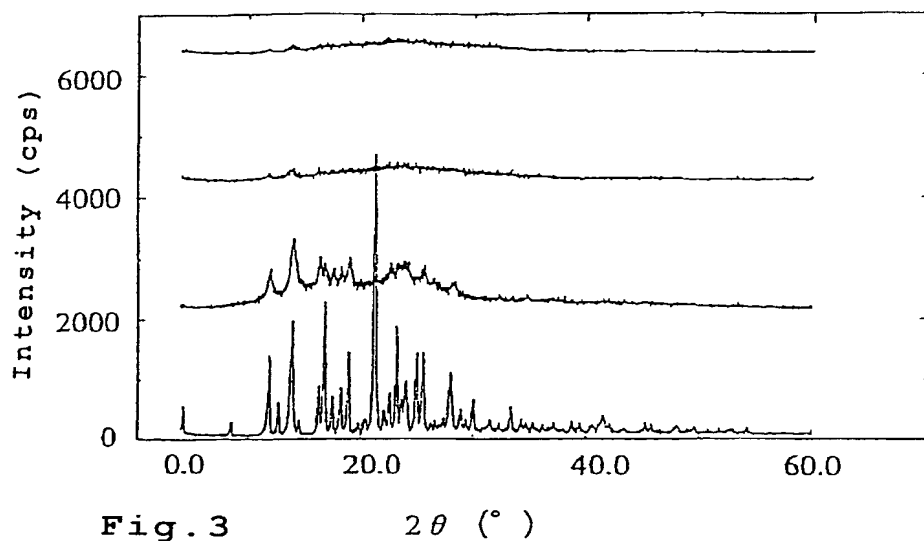


Fig. 3

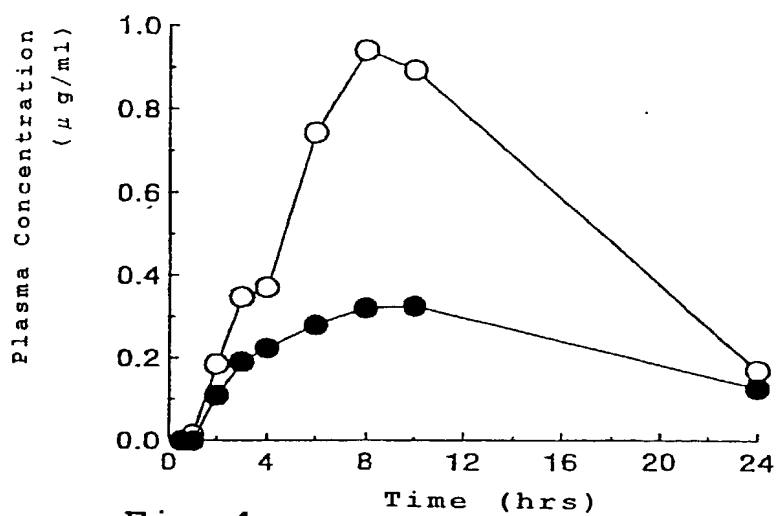
 $2\theta (^{\circ})$ 

Fig. 4

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Declaration and Power of Attorney for Patent Application

特許出願宣言書及び委任状

Japanese Language Declaration

日本語宣言書

私は、以下に記名された発明者として、ここに下記の通り宣言する：

As a below named inventor, I hereby declare that:

私の住所、郵便の宛先そして国籍は、私の氏名の後に記載された通りである。

My residence, post office address and citizenship are as stated next to my name.

下記の名称の発明について、特許請求範囲に記載され、且つ特許が求められている発明主題に関して、私は、最初、最先且つ唯一の発明者である（唯一の氏名が記載されている場合）か、或いは最初、最先且つ共同発明者である（複数の氏名が記載されている場合）と信じている。

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Method For Pulverizing To Fine

Powder

上記発明の明細書はここに添付されているが、下記の額がチェックされている場合は、この限りでない：

the specification of which is attached hereto unless the following box is checked:

☐ _____ の日に出願され、
この出願の米国出願番号またはPCT国際出願番号は、
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I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

私は、連邦規則法典第37編規則1.56に定義されている、特許性について重要な情報を開示する義務があることを認める。

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

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Prior Foreign Application(s)
外国での先行出願

Priority Not Claimed
優先権主張なし

Hei-11/116,810

Japan

23/04/99

(Number)
(番号)

(Country)
(国名)

(Day/Month/Year Filed)
(出願日/月/年)

☐

(Number)
(番号)

(Country)
(国名)

(Day/Month/Year Filed)
(出願日/月/年)

☐

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(Application No.)
(出願番号)

(Filing Date)
(出願日)

(Application No.)
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(出願日)

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(Application No.)
(出願番号)

(Filing Date)
(出願日)

(Status: Patented, Pending, Abandoned)
(現況: 特許許可、係属中、放棄)

(Application No.)
(出願番号)

(Filing Date)
(出願日)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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(日本語宣言書)

委任状： 私は本出願を審査する手続を行い、且つ米国特許商標庁との全ての業務を遂行するために、記名された発明者として、下記の弁護士及び／または弁理士を任命する。(氏名及び登録番号を記載すること)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith (list name and registration number).

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Direct Telephone Calls to: (name and telephone number)

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3-00

Full name of sole or first inventor

発明者の署名

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Inventor's signature

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Full name of second joint inventor, if any

第二共同発明者の署名

日付

Second inventor's signature

Date

住所

Residence

国籍

Citizenship

郵便の宛先

Post Office Address

(第三以下の共同発明者についても同様に記載し、署名をすること)

(Supply similar information and signature for third and subsequent joint inventors.)